Dasatinib-induced chylothorax in chronic myeloid leukemia

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Pulmonary adverse events are common abnormalities associated with the use of dasatinib in chronic myeloid leukemia. We present a case of a 69-year-old man who suddenly developed a rare chylothorax pulmonary adverse event following 10 months of dasatinib treatment.

Dasatinib is a second-generation potent and efficacious oral tyrosine kinase inhibitor, frequently used for imatinib-resistant or -intolerant *BCR-ABL*–positive chronic myeloid leukemia (CML) and for Philadelphia chromosome–positive acute lymphocytic leukemia (1). Pulmonary adverse events are reported in about 35% of patients. The most common pulmonary abnormalities associated with dasatinib include pleural effusion, pulmonary hypertension, and parenchymal opacities. Dasatinib-related chylothorax is an uncommon pulmonary adverse event.

CASE PRESENTATION

A 69-year-old man with CML for 5 years presented complaining of progressive dyspnea for about 5 days. He had previously been treated with imatinib and nilotinib. Imatinib was stopped due to treatment failure, while nilotinib was discontinued due to intolerable side effects despite dose reduction. He had been on dasatinib 100 mg once daily for about 10 months, which he seemed to tolerate well. On presentation, his vital signs were stable, but he remained dyspneic, worse on exertion. He had diminished breath sounds and increased egophony on his right side. A chest radiograph showed a pleural effusion, more prominent on his right side. His previous chest radiographs were normal. A subsequent chest computed tomography scan showed a moderate amount of fluid in his pleural space compromising the right lung without any adenopathy or lung masses *(Figure 1)*. Thoracentesis revealed 1 L of thick milky-appearing fluid *(Figure 2)*. Pleural fluid analysis showed a predominance of lymphocytes (90%) and a lactate dehydrogenase level of 120 U/L, glucose of 157 mg/dL, protein of 4.8 g/dL, amylase of 39 U/L, and triglycerides of 405 mg/dL. Adenosine deaminase was 15 U/L. Fungal, bacterial, and AFIB cultures were reported as negative.

Following thoracentesis, the patient's dyspnea improved. A repeat chest radiograph showed no pneumothorax with improvement in his effusion. He was under observation for 24 hours prior to discharge and was advised to continue his dasatinib. He returned to our institution a few months later with similar symptoms requiring a therapeutic thoracentesis. His dasatinib dose was gradually decreased to 50 mg orally once daily, but continued to lead to symptomatic pleural effusions. He was switched to bosutinib and has been tolerating therapy well without any symptoms. He continues to follow up with our oncology and pulmonary services.

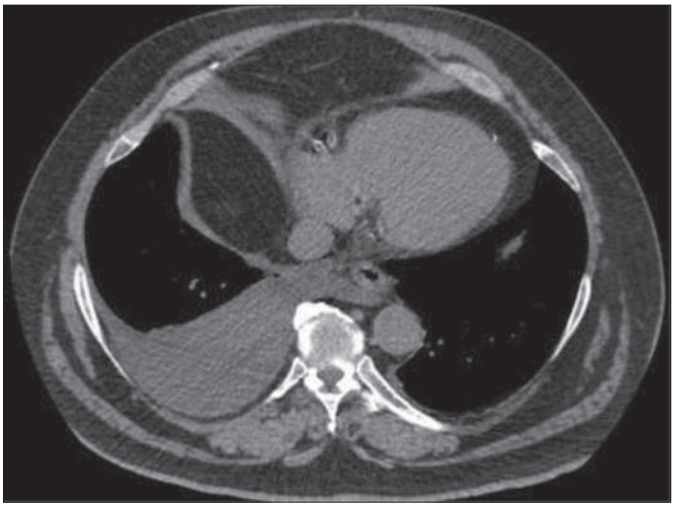

Figure 1. Chest computed tomography scan showing a moderate amount of fluid in the patient's pleural space compromising the right lung without any adenopathy or lung masses.

DISCUSSION

Here we present a rare case of dasatinib-induced chylothorax in a patient with CML. The patient's history and thorough workup, including a CT scan of the chest, did not suggest any other possible etiology.

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Figure 2. One liter of thick milky-appearing fluid resulting from thoracentesis.

Chylothorax typically results from disruption of the normal lymphatic flow, such as insult to the thoracic duct or its tributaries, causing leakage of lymphatic fluid into the thoracic cavity. Malignancy-induced thoracic duct obstruction is the leading cause of chylothorax, with most malignancies being lymphomas (70% of which are Hodgkin lymphomas) (2, 3). Generally, causes of chylothorax can be divided into traumatic or nontraumatic etiologies. Traumatic cases can then be further subdivided as iatrogenic or noniatrogenic (4). Iatrogenic traumatic causes include thoracic duct damage following subclavian vein catheterization and duct blockage due to central venous catheterization–related venous thrombosis (5). Noniatrogenic traumatic cases include thoracic duct damage following fracture, dislocation of the spine, childbirth, and penetrating trauma from knife or gunshot injuries (6, 7). Nontraumatic etiologies include malignancy, sarcoidosis, retrosternal goiter, amyloidosis, superior vena cava thrombosis, benign tumors, congenital duct abnormalities, and diseases of the lymph vessels such as yellow nail syndrome, lymphangioleiomyomatosis, and hemangiomatosis (4).

Dasatinib-induced chylothorax is a rare yet poorly understood phenomenon. Evidence suggests that microscopic disruptions in lymphatic channels lead to chylous effusions following dasatinib therapy rather than macro-level classical thoracic duct involvement. Despite the multiple heterogenous etiologies for the development of chylothorax, dasatinib is the only drug known to be associated with this adverse effect. The development of chylothorax during dasatinib therapy may not be drug related. A few metastatic prostate cancer patients receiving dasatinib therapy also developed chylothorax. Pleural fluid analysis demonstrated positive cytology. Therefore, the full course of chemotherapy was completed. In these patients, a significant clinical response was documented with complete resolution of chyle effusion despite no change in dasatinib therapy (8).

Dasatinib-related pleural exudative, transudative, and chylous effusions are all lymphocyte-predominant exudates (9). Possible mechanisms have been identified that may explain these effusions. The tyrosine kinase platelet-derived growth factor receptor beta (PDGFR-β) on pericytes regulates postnatal angiogenesis, lymphangiogenesis, mesangial and vascular smooth muscle cell proliferation, and pericyte recruitment to capillaries. Potent inhibition of PDGFR-β can result in significant fluid retention and microangiopathy and lead to defective vascular remodeling (10, 11). Similarly, inhibition of tyrosine kinases that are responsible for capillary integrity may be implicated, especially if they are overexpressed in the pulmonary vasculature and/or pleural epithelium. Src is a protooncogene encoding a nonreceptor tyrosine kinase, which belongs to a family of 11 nonreceptor tyrosine kinases collectively known as the Src family kinases. Yes and Src are members of this family and are widely expressed in hematopoietic cells in lung tissue (12, 13). Vascular permeability is mediated by vascular endothelial growth factor, which is directly dependent on Yes and on Cellular Src (c-Src), both of which are inhibited by dasatinib (14, 15). c-Src also independently regulates focal adhesions and adherens junctions, both of which are key in regulating cell adhesion (16, 17). It is interesting that dasatinib may target c-Src tyrosine kinases and is being used in clinical trials for non-Hodgkin lymphoma, metastatic breast carcinoma, and prostate carcinoma in addition to CML and Philadelphia chromosome–positive acute lymphocytic leukemia. Although the development of pleural effusions and chylous effusions present similarly with respiratory compromise and share possible biological mechanisms, they are considered separate distinct clinical adverse effects.

Chylothorax is defined according to Light's criteria as a turbid pleural effusion with triglycerides >110 mg/dL (18, 19). A visual inspection of the pleural fluid should be conducted, and milky pleural fluid should always be investigated for chylothorax. Not all chylothorax is exudative, with 20% of cases being transudative (20, 21). An important distinction should also be made between chylothorax and pseudochylothorax based on cholesterol and triglyceride concentrations (22). Pseudochylothorax consists primarily of cholesterol derived from longstanding pleural fluid cell debris. Pleural fluid cholesterol >200 mg/dL (5.18 mmol/L) with a pleural fluid triglyceride <50 mg/dL (0.56 mmol/L) is more likely pseudochylothorax. Chylothorax presents with concentrations of triglycerides in the pleural fluid >110 mg/dL (1.24 mmol/L) and with cholesterol concentrations <200 mg/dL (5.18 mmol/L). Pleural fluid findings should not be interpreted in isolation; rather, the clinical history and presentation should also be taken into account.

Although treatment discontinuation leads to symptom resolution, in certain cases dose reduction has produced the same effect (23). Given the therapeutic benefits of dasatinib therapy in the post-imatinib setting, initial efforts should be focused on treating the chylothorax by attempting dose reduction as opposed to discontinuing dasatinib altogether. Transiently discontinuing dasatinib until chest tube drainage and

supportive care measures achieve symptomatic improvement followed by dasatinib dose reduction has been suggested. In addition, the use of short-term steroids and diuretics has also been shown to be helpful (9). In our case, dose reduction alone was not sufficient, and switching from dasatinib to bosutinib was eventually required.

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